Highlights from other journals – February 2001

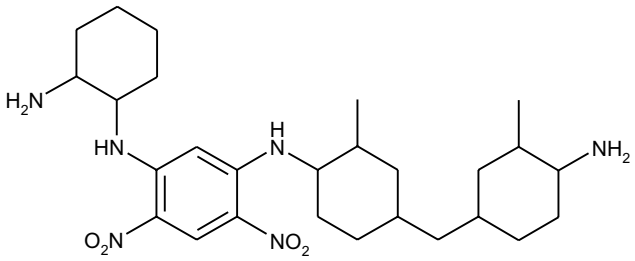
Small molecule enzyme inhibitors

In recent years, the rate of accumulation of genomic sequence information has rapidly accelerated, culminating in the sequencing of the human genome. This information has aided in the identification of genes whose products could serve as targets for pharmacological intervention. Although the accumulation of sequence information has been rapid, functional information for the corresponding gene products has lagged behind. For example, 40% of the open reading frames in *Escherichia coli* encode proteins of unknown function, even though this microbe has been scrutinised for decades. This lack of functional information makes it difficult to develop assays to exploit these genes as potential drug targets. Techniques and tools to facilitate the screening process independent of functional assays are needed to efficiently exploit available targets. A combinatorial approach was used to synthesise peptide libraries with a complexity of more than 5 x 10^8 members per library, arising from either 7- or 12-residue peptides in a random 12-mer library, or random 11-residue peptides in which the central residue of each library was fixed with a different residue (Detection of small-molecule enzyme inhibitors with peptides isolated from phage-displayed combinatorial peptide libraries *Chemistry & Biology*, 7, (2000), 17-25). A broad range of enzymes were selected as targets for phage display and a series of peptides isolated that bound specifically to each target. This methodology is useful in formatting assays for enzyme targets. The active peptides identified can be used in simple competitive binding assays to identify small-molecule inhibitors of enzyme function, targeting the same functional sites on enzymes to which effective therapeutic agents must be targeted. The binding assay can be used with a variety of detection systems and is readily adaptable to automation, making this platform suitable for high-throughput screening of compound libraries for drug discovery.

Antibacterial compounds

Gram positive bacteria have become increasingly resistant to antimicrobial agents and multi-drug resistant bacterial pathogens have now become a major problem in clinical medicine. *S. aureus* is a common human pathogen that has become increasingly difficult to treat because of resistance to antimicrobial agents. Vancomycin remains the main antimicrobial treatment for infections caused by *S. aureus* strains that are resistant to pencillinase-resistant antibiotics. The emergence of vancomycin-resistant *Enterococcus* species raises the threat of possible transfer of resistance factors to *S. aureus*. Vancomycin-resistant *Stapylococcus* clinical isolates have already been discovered in Japan. There is, therefore, a need for new antimicrobial agents. A solution phase approach was used to identify compounds which have novel antibacterial activity (Solution-phase synthesis of a 1,5-dialkylamino-2,4-dinitrobenzene library and the identification of novel antibacterial compounds from this library, K. S. Lam *et. al., J. Comb. Chem.*, 2, (2000), 467-474). A library of 4900 compounds was prepared in mixtures of 10 from a solution phase sequential displacement of two fluorines on the 1,5-difluoro-2,4-dinitrobenzene core library template using a set of 70 amines. The mixtures of 10 were tested for antibacterial activity against *Staphylococcus aureus* and *Enterococcus faecalis* which identified several active mixtures. All compounds contained within the mixtures were resynthesised as single compounds and re-tested. One of the most potent compounds isolated was (i) which possessed a minimum inhibitory concentration (MIC) and minimum bactericidal

concentration (MBC) against *S. aureus* of 11.09 and 22.18 µg/mL respectively, and an MIC and MBC against *E. faecalis* of 5.5 and 11.0 µg /mL respectively. This work may therefore prove useful in the further optimisation of the lead compounds identified in this library for the production of even more potent novel antibacterial agents.



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